



Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 12/21/2016

Visit the AIDSinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

Integrase Inhibitors

Glossary of Terms for Supplement

Carcinogenic: Producing or tending to produce cancer

- Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
- Genetic mutations and/or chromosomal damage can contribute to cancer formation.

Clastogenic: Causing disruption of or breakages in chromosomes

Genotoxic: Damaging to genetic material such as DNA and chromosomes

Mutagenic: Inducing or capable of inducing genetic mutation

Teratogenic: Interfering with fetal development and resulting in birth defects

This class of antiretroviral (ARV) drugs inhibits integrase, the viral enzyme that catalyzes the two-step process of insertion of HIV DNA into the genome of the human cell. Integrase catalyzes a preparatory step that excises two nucleotides from one strand at both ends of the HIV DNA and a final “strand transfer” step that inserts the viral DNA into the exposed regions of cellular DNA. The integrase inhibitor drug class targets this second step in the integration process. Integration is required for the stable maintenance of the viral genome as well as for efficient viral gene expression and replication. Integrase also affects reverse transcription and viral assembly. Host cells lack the integrase enzyme. Because HIV integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV that is resistant to other classes of ARV drugs.

Dolutegravir (Tivicay, DTG)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Dolutegravir is classified as Food and Drug Administration Pregnancy Category B.

Animal Carcinogenicity Studies

Dolutegravir was not genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in 2-year long-term studies in mice at exposures up to 14-fold higher than that achieved with human systemic exposure at the recommended dose, or in rats at exposures up to 10-fold higher in males and 15-fold higher in females than human exposure at the recommended dose.

Reproduction/Fertility

Dolutegravir did not affect fertility in male and female rats and rabbits at exposures approximately 27-fold higher than human clinical exposure, based on area under the curve, at the recommended dose.

Animal Teratogenicity/Developmental Toxicity

Studies in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity or effect on reproductive function with dolutegravir.

Placental and Breast Milk Passage

Studies in rats have demonstrated that dolutegravir crosses the placenta in animal studies and is excreted into breast milk in rats.

Human Studies in Pregnancy

Pharmacokinetics

Human reports of dolutegravir use in human pregnancy are limited to two published case reports of dolutegravir use in single pregnant women and one presentation of dolutegravir safety, pharmacokinetic, and efficacy data from 21 pregnant women.¹⁻³ In both case reports, dolutegravir was used safely and effectively in pregnancy.^{1,2} In the series of 21 pregnant women, dolutegravir plasma concentrations were lower during

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 12/21/2016

pregnancy than postpartum but HIV-1 RNA in the third trimester was below 50 copies/mL in all 15 women for whom third-trimester data were available. Dolutegravir was well tolerated by these pregnant women.³

Placental and Breast Milk Passage

No human data on placental passage or breast milk excretion are available.

Teratogenicity Data

In the Antiretroviral Pregnancy Registry, insufficient numbers of first-trimester exposures to dolutegravir in humans have been monitored to be able to make a risk determination.⁴ In the series of pregnant women discussed above, congenital anomalies were reported in 4 infants: total anomalous pulmonary venous return, cystic fibrosis and polycystic right kidney, congenital chin tremor, and sacral dimple with filum terminale fibrolipoma.

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Dolutegravir (DTG) <i>Tivicay</i>	<u>Tablets:</u> • 50 mg	<u>Standard Adult Dose</u> <i>ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive Patients)</i>	Unknown placental transfer to fetus.
(DTG/ABC/3TC) <i>Triumeq</i>	<u>Triumeq:</u> • DTG 50 mg plus ABC 600 mg plus 3TC 300 mg tablet	<u>DTG (Tivicay):</u> • 1 tablet once daily, without regard to food. <u>DTG/ABC/3TC (Triumeq):</u> • 1 tablet once daily, without regard to food. <i>ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced</i> <u>DTG (Tivicay):</u> • 1 tablet twice daily, without regard to food. <u>PK in Pregnancy:</u> • Limited PK data in human pregnancy. <u>Dosing in Pregnancy:</u> • Insufficient data to make dosing recommendation.	Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits.

^a Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, Appendix B, Table 7](#)).

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; DTG = dolutegravir; EFV = efavirenz; FPV/r = fosamprenavir/ritonavir; PK = pharmacokinetic; TPV/r = tipranavir/ritonavir

References

1. Pain JB, Le MP, Caseris M, et al. Pharmacokinetics of dolutegravir in a premature neonate after HIV treatment intensification during pregnancy. *Antimicrob Agents Chemother*. 2015;59(6):3660-3662. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25845873>.
2. Pinnetti C, Tintoni M, Ammassari A, et al. Successful prevention of HIV mother-to-child transmission with dolutegravir-based combination antiretroviral therapy in a vertically infected pregnant woman with multiclass highly drug-resistant HIV-1. *AIDS*. 2015;29(18):2534-2537. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26372490>.
3. Mulligan N, Best B, Capparelli E, et al. Dolutegravir pharmacokinetics in HIV-infected pregnant and postpartum women. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA.
4. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 Jan 1989–31 July 2015. Wilmington, NC: Registry Coordinating Center. 2015. Available at <http://www.apregistry.com/>.